AD_____

Award Number: DAMD17-98-1-8240

TITLE: Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal Body Composition and Behavioral Mechanisms

PRINCIPAL INVESTIGATOR: Nagi B. Kumar, Ph.D.

CONTRACTING ORGANIZATION: University of South Florida
Tampa, Florida 33620

REPORT DATE: September 2000

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2000	Annual (1 Sep 99 - 31 Aug 00)

4. TITLE AND SUBTITLE
Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal Body Composition and Behavioral Mechanisms

5. FUNDING NUMBERS
DAMD17-98-1-8240

6. AUTHOR(S)
Nagi B. Kumar, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of South Florida
Tampa, Florida 33620

E-MAIL:
kumar@moffitt.usf.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

The purpose of the study is to observe the relative contribution of thyroid function, sex-hormonal levels, physical activity, psychological state and nutritional intake on changes in body weight in a group of breast cancer patients, receiving adjuvant chemotherapy.

Women scheduled to receive adjuvant chemotherapy were assessed prior to their first infusion and followed until the end of treatment and changes in weight, body composition, physical activity, nutritional intake, fatigue, sex-hormones, thyroid hormones and ways of coping were observed. Fifty-three subjects completed the study during the first year. Preliminary results indicate that the average age of this cohort is 48.96 years, 43.9% were smokers, 48% had a family history of breast cancer, 56% reported increased fatigue and 55% gained weight during chemotherapy. Hyperphagia was observed during treatment, with percent fat intake increasing from 26% to 30.2% by the end of therapy. However, we observed a significant decrease in the average hours worked from 33.4 hours per week to 12.7 hours by the end of therapy. Fifty five percent of the subjects were pre-menopausal at baseline, but all patients were amenorrheic at the completion of therapy with 72.5% showing a significant decrease in serum total estradiol levels post therapy. Thyroxine-binding-globulin levels were elevated in 68.8% of the subjects after therapy while Triiodothyronine-3 uptake levels were decreased indicative of lowered thyroid function. Based on the preliminary observations, weight gain in breast cancer patients may be a phenomenon resulting from hormonal and lifestyle changes and offers an opportunity for prevention and improved prognosis.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer, Chemotherapy, Weight Gain	23
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

Table of Contents

Front Cover.....1
Standard Form(SF) 298, Report Documentation Page.....2
Table of Contents.....3
Introduction.....4
Body.....5-6
Key Research Accomplishments.....7-8
Conclusions.....9
References.....10-11
Appendices.....12-23

Introduction:

Weight Gain in Breast Cancer Patients on Chemotherapy

It is estimated that over 182,800 new cases of female breast cancer will be diagnosed in the United States in 2000 and 41,200 will die of this disease.[1] Most of these patients will be diagnosed with stage I or II disease, and a significant proportion of these women will be treated with chemotherapy in addition to surgery and/or radiation therapy. Although the benefits of adjuvant chemotherapy and radiation therapy are well established, and although several side effects such as cancer cachexia challenge the health professionals, one of the most distressing side effect as reported by patients is weight gain.[2-8] Weight gain in this population may prove to be a more serious side effect than others, since it can not only decrease quality of life but may potentially increase rate of recurrence and threaten long-term survival.[7, 9-11] The impact of weight gain may be even more profound, because it may predispose women to heart disease, diabetes, gall bladder disease, endometrial cancer and orthopedic disturbances. These chronic illnesses may pose a greater concern, since women with early stage breast cancer will be cured of the disease but may suffer long term negative consequences as a result of treatment.

Prevalence and Magnitude of Weight Gain in Breast Cancer Patients During Chemotherapy: Weight gain, anywhere from 5-50lbs in breast cancer patients receiving adjuvant therapy has now been documented consistently for the past two decades.[12-13] Significant weight gain occurred in 50-96% of all breast cancer patients receiving adjuvant chemotherapy[3] irrespective of stage of disease, more so among premenopausal women compared to post menopausal women.[9] In addition, significant gain in weight has been observed in patients receiving prednisone as a chemotherapeutic regimen[14-15] or when multiple agents are used[10, 12] compared to single agent therapies. Bonadonna et al found that longer duration of chemotherapy increased the total amount of weight gained[16] and oral agents produce greater weight gains than infusion-based therapies.[17]

Consequences of Weight Gain: More recent findings suggest that obesity at time of diagnosis is an adverse prognostic indicator even after the administration of chemotherapy.[18] We and other have observed that obesity in postmenopausal node positive patients was a negative prognostic indicator[15, 19] and the risk for disease recurrence among obese patients was 1.33-1.5 times that of the non-obese population.[9, 18] Camoriano, in addition reported 1.6 times greater risk of death in premenopausal women who gained weight.[9]

Possible Mechanisms: While the cause of weight gain in breast cancer patients remains unknown it, is most likely a result of several contributing factors. Some proposed explanations include psychological factors such as change in coping mechanisms leading to a change in eating behavior, change in activity level due to fatigue or disruption of normal lifestyle, hormonal changes, and the metabolic effects of chemotherapy or radiotherapy.

Purpose:

The purpose of this study is to prospectively and systematically observe the relative contribution of each viable mechanism such as nutritional intake, activity levels, body composition, hormonal function, thyroid function, coping mechanisms and fatigue scores on weight gain in breast cancer patients on chemotherapy.

Objectives

Specific Aim 1: To characterize the severity and course of weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 2: To examine the impact of chemotherapy-induced change in activity levels on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 3: To examine the effect of chemotherapy-induced hyperphagia on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 4: To examine the effect of chemotherapy-induced sex-hormone level changes on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 5: To examine the effect of chemotherapy-induced change in thyroid function on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 6: To systematically investigate the relative contribution of thyroid function, sex-hormonal levels, physical activity, body composition, psychological state and nutritional intake on changes in body weight in a group of pre-menopausal and post-menopausal stage I-III breast cancer patients, receiving adjuvant chemotherapy.

Key Research Accomplishments:

As planned and described in the Statement of Work, Task 1 of recruitment and data collection and Task 2 - abstraction of Medical record data during months 1-30, of which moths 0-23 is currently reported, has been successful, thus far.. The first two months of the study was spent organizing (a) Instruments and procedures to be used in the study, (b) Consent form and procedures, (c) establishing procedures for recruitment from various medical oncology clinics at the cancer Center, (d) timely, safe blood draws thus preventing duplication of draws, (d) preventing any additional patient visit to the center, (e) collaboration with lab to plan for safe, accurate and timely handling of blood and transport.

Task 1: Subject Recruitment: The patient sample selected for the study is to include a total of 200 consecutive pre-menopausal and post-menopausal patients recruited over a 36 month period, with primary, operable, Stage I to IIIB, axillary lymph node positive and negative breast cancer patients who have consented to be treated using one of two adjuvant or systemic chemotherapy protocols at the H. Lee Moffitt Cancer Center & Research Institute during the study period. Women, of all races and ethnicity, between ages 25 and 75, and breast cancer patients who will receive at least 75% Cytoxan, Methotextrate, 5FU (CMF), Cytoxan, Cytoxan, Adriamycin and 5FU(CAF) or Cytoxan and Adriamycin (CA) chemotherapy regimens with or without radiation therapy at first screening contact will be admitted to the study. Currently 115 subjects have been recruited, of whom 77 have completed the 6 month treatment/observation phase of the study, and an additional 26 subjects are currently active in this protocol. As predicted we had twelve (12) dropouts in the study, six (6) were unable to complete their activity records, three(3) of whom did not wish to participate, one (1) too ill to complete monitors and 2 were eliminated from the study as the final treatment plan did not include adjuvant chemotherapy. We have thus successfully recruited almost 60% of the sample planned for the study, in a period of 20 months.
Data Collection: Upon recruitment, and upon receiving consent from subjects, the following data were collected, as planned:
1.Confirmation of the accuracy of eligibility information, including the using an initial screening form.

2.Demographic information, personal and medical history, hormonal and reproductive history, exercise, smoking and alcohol use history will be obtained by an RD using the Epidemiological Questionnaire.
3.Anthropometric measurements such as subject's height, weight, skinfolds and circumference measurements.
4.Twenty (20) ml of blood will be drawn into heparinized tubes in a non-fasting state at the same time of day, between 7:00 AM and 12:00 noon, for each individual to obtain 10 ml of serum for analysis of total and free estradiol, sex-hormone binding globulin, T4 and thyroid binding globulin assessment for T3 uptake.
5.Subjects will be asked to complete a self-administered version of the Stanford-five city Project Questionnaire to monitor Activity Levels.
6. Standard 4-day diet record(FDFR).
7. Menstrual histories will be obtained from all peri- and pre-menopausal subjects. This information will be recorded on the FDFR.
8.The Profile of Mood States Fatigue Subscale (POMS-F), a scale to measure fatigue (Appendix 6) will be used to quantify fatigue in these subjects.[37]
9.The Ways of Coping Checklist (WOCC) consists of 66 items that describe a broad range of cognitive and behavioral strategies people use to manage internal and/or external demands in specific stressful encounters defined here as breast cancer treatment, will be used.[38]

We have observed that several patients have had difficulty completing the 4-day food records during the 3 to 4 chemotherapy treatments. During those situations, the research team has been able to obtain a 24-hour recall or a 2-day record of intake from the patient or a family member. Apart from this instrument, we have had excellent compliance to completion of serial information from our breast cancer patients.

Task 2: Abstraction of Medical Record Data:
Upon completion of the study, data regarding patient's disease related prognostic indicators is currently being extracted from their medical chart. Quality control procedures for data collection and abstraction have been ongoing. We are currently continuing to obtain information on tumor size, ER/PR positivity, DNA ploidy status and proliferative indices such as Ki-67, which are routinely available for this group of patients. Abstraction of medical records data has been completed for 77/115 patients, who have completed the observational period of the study.

Nutritional Intervention in Patients post completion of the study period:
As reported in our initial report, upon completion of the study, we have felt the need for and have had several requests from medical oncologists and patients for continued follow-up of patients who have gained weight during chemotherapy. We have established a structured "Moffitt Weight Management Program", which is currently offered as a pilot program, specifically for this post-treatment Breast Cancer Patient group to enable them to successfully manage weight, post-treatment. The program includes 8-1 hour sessions and incorporates body composition and nutritional analysis, Behavior Management, Assessing fitness and incorporating physical activity and improving food choices towards long-term weight management. This program has also included clientile from the Lifetime Cancer Screening Program, include those women who have been genetically screened as high risk for breast cancer.

Data Entry & Analysis:
Data entry has been initiated since November 1999 and all pertinent data with regard to patients who have completed the study to date have been entered into this data bank. Quality control procedures for data entry continues to be applied, as planned. Preliminary results were analyzed in May 2000. We plan perform the second preliminary data analysis in October 2000.

Results:
To date, 115 subjects have been recruited, of whom 77 have completed the 6 month treatment/observation phase of the study, and an additional 26 subjects are currently active in this protocol. Preliminary data analysis of fifty-three (53) subjects who were recruited during the first 15 months of the study was completed.

Preliminary results indicate the following:

- The average age of this cohort is 48.96 years
- 43.9% were smokers
- 48% had a family history of breast cancer
- 56% reported increased fatigue
- 55% gained weight during chemotherapy.
- Hyperphagia was observed during treatment with increase in calories and fat intake
- Percent fat intake increased from a baseline intake of 26% of total calories to 30.2% by the end of therapy in this breast cancer patient group.
- A significant decrease in the average hours worked from 33.4 hours per week to 12.7 hours by the end of therapy was observed
- 100% of subjects reported fatigue
- Fifty five percent of the subjects were pre-menopausal at baseline
- All patients were amenorrheic at the completion of therapy
- 72.5% showing a significant decrease in serum total estradiol levels post therapy
- Thyroxine-binding-globulin levels were elevated in 68.8% of the subjects after therapy
- Triiodothyronine-3 uptake levels were decreased indicative of lowered thyroid function.

Based on the preliminary observations, as hypothesized, weight gain in breast cancer patients may be a phenomenon resulting from hormonal and lifestyle changes and offers an opportunity for prevention and improved prognosis. We observed hyperphagia, lowered physical activity, amenorrhea, fatigue in this patient population, which may all contribute to weight gain. Android obesity and adult weight gain are known risk factors of survival in breast cancer patients. As the cause of weight gain is preventable, by educating and counseling patients during treatment, weight gain in breast cancer patients can be prevented, thereby improving prognosis.

Reportable Outcomes:
Preliminary results of this study has been presented as an abstracts (Appendix 1), poster session (Appendix 2) and will be presented in a plenary session (Appendix 3) in the following National and International Meetings:

1. Kumar NB, Riccardi D, Allen K, Cantor A, Jacobsen P. Horton J, Minton S, Balducci & Lyman GH. Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal, Body Composition and Behavioral Mechanisms. Proc of the US Army Breast Cancer research Program Meeting, Era of Hope, 2000. (Appendices 1 & 2)
2. Kumar NB, Riccardi D, Allen K, Cantor A, Jacobsen P. Horton J, Minton S, Balducci L & Lyman GH. Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal, Body Composition and Behavioral Mechanisms. Abstract accepted for Podium Presentation, Proceedings of the 5th International Symposium on Predictive Oncololgy & Therapy. November 2-5, 2000. (Appendix 3)

Conclusions:
Definitive prospective studies such as ours, that systematically observes the relative contribution of each viable mechanism such as nutritional intake, activity levels, body composition, hormonal function, thyroid function, coping mechanisms and fatigue scores during chemotherapy on weight gain are needed. While it is important to initiate action to prevent the problem of weight gain in breast cancer patients, an essential first step to intervention or rehabilitation is to identify the mechanisms by which weight gain occurs which may hasten the development of effective intervention strategies for weight management for specific regimens. In our current longitudinal research study, we are exploring the impact of adjuvant chemotherapy for breast cancer treatment on these clinical and psychological outcomes and identify systematically the mechanisms and offer opportunities for delivering effective care to prevent and facilitate recovery from breast cancer.

In a recent study that was published by our group (Appendix 4), eighty-three of 166 breast cancer patients with up to 10 years of follow-up failed to survive. Android body fat distribution, as indicated by higher suprailliac: thigh ratio was a statistically significant ($P<0.0001$) prognostic indicator for survival after controlling for stage of disease, with a hazard ratio of 2.6 (95% CI, 1.63 - 4.17). Adult weight gain, as indicated specifically by weight at age 30, was a statistically significant ($P<0.05$) prognostic indicator for survival with a hazard ratio of 1.15 (95% CI, 1.0 - 1.28). In addition, we observed Quatelet Index, a negatively significant ($P<0.01$) prognostic indicator for survival with a hazard ratio of 0.92 (95% CI 0.87 - 0.98). Based on the relevant literature and the preliminary results of our study, we hypothesize that weight gain will occur in a significant number of breast cancer patients on adjuvant chemotherapy and in addition that this weight gain will be a result of hyperphagia, significant lowering of activity level, decrease in free and total estradiol levels, similar to the hormonal milieu of menopause which is known to alter body composition and appetite and lowering of thyroid function resulting in decreased activity levels, all contributing to weight gain in this population. As weight gain in this population is a risk factor for survival, it is critical to explore the impact of adjuvant chemotherapy for breast cancer treatment on these clinical and psychological outcomes and identify systematically the mechanisms and offer opportunities for delivering effective care to prevent and facilitate

recovery from breast cancer, which will further the programmatic goals of the BCRP of the Department of Defense. Our research may in addition lead to the elucidation of hormonal markers that predict the probability of disease recurrence. This may also establish the mechanisms by which weight gain has an impact on the neoplastic process. If changes in body weight, body composition, hormonal levels, psychological health, dietary and other lifestyle factors alter prognosis, manipulation of these variables by intervention and counseling may improve prognosis, facilitate recovery from breast cancer and the credibility of such interventions will be enhanced.

Bibliography

1. American Cancer Society,Inc. (2000). Cancer Facts & Figures-2000.(ACS Publication) Atlanta, GA.
2. Knobf MK, Mullen JC, Xistris D, Mortiz PA. Weight gain in women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum. 10:28-34, 1983.
3. Huntington MO. Weight gain in patients receivng adjuvant chemotherapy for carcinoma of the breast. Cancer. 56:472-474, 1985.
4. Boyd NF. Nutrition and Breast Cancer. J Natl Cancer Inst. 85:6-7, 1993.
5. Prozato P et al. Megasterol acetate:phase II study of a single daily adminstration in advanced breast cancer. Breast Cancer Res treat. 17:51-54, 1990.
6. Dixon J, Moritz D, and Baker F: Breast Cancer and Weight Gain; An Unexpected Finding. Oncology Nursing Forum 5:5-7, 1978.
7. Demark-Wahnefried W, Winer EP, and Rimer, BK: Why women Gain Weight With Adjuvan Chemotherapy for Breast Cancer. Journal of Clinical Oncology 11:1418-1429, 1993.
8. Levine EG, Racqynski JM, Carpenter JT: Weight Gain With Breast Cancer Adjuvant Treatment. Cancer 67: 1954-1959, 1991.
9. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, and Veeder MH: Weight Change in Women Treated With Adjuvant Therapy or Observed Following Mastectomey for Node-Positive Breast Cancer. Journal of Clinical Oncology 8:1327-1334, 1990.
10. Chlebowski RT, Weiner JM, Reynolds R, et al: Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Research and Treatment 7:23-29, 1986.
11. Cruz JM, Muss HB, Brockschidt JK, Evans G. Weight changes in women with metastatic breast cancer treated with megasterol acetate: a comparison of standard versus high-dose therapy. Semin Oncol. 17:63-67, 1990.
12. Heasmand KZ, Sutherland HJ, Campbell JA, et al: Weight gain during adjuvant chemotherapy for breast cancer. Breast Cancer Research and Treatment 5:195-200.
13. Huntington MO: Weight Gain in Patients Receiving Adjuvant Chemotherapy for Carcinoma of the Breast. Cancer 56:472-474, 1985.
14. DeConti RC. Weight gain in the adjuvant chemotherapy of breast cancer. Proc Am Soc Clin Oncol. 1:73, 1982.
15. Goodwin PJ, Panzarella T and Boyd NF: Weight gain in women with localized breast cancer- a descriptive study. Breast Cancer Research and Treatment 11:59-66, 1988.
16. Bonadonna G, Valagussa P, and Rossi A: Ten-year experience with CMF based adjuvant chemotherapy in resectable breast cancer. Breast Cancer Research and Treatment 5:95-115, 1985.
17. Knobf M: Physical and psychological distress associated with adjuvant chemotherapy in women with breast cancer. 4:678-684, 1986.
18. Bastracchea J, Hortobagyi GN, Smith TL, Kau SC: Obesity as an Adverse Prognostic Factor for Patients Receiving Adjuvant Chemotherapy for Breast Cancer. Annals of Internal Medicine 119: 18-25, 1993.
19. Schapira DV, Kumar NB, Lyman GH, Cox CE: Obesity and Body Fat Distribution and Breast Cancer Prognosis. Cancer 67: 523-528, 1991.

20. Demark-Wahnefried W, et al. Reduced rates of metabolism and decresed physical activity in breast cancer patients receiving adjuvant chemotherapy. Am J Clin Nutr. 65:1495-501, 1997.
21. DeGeorge D, Gray JJ, Fetting JH, and Rolls BJ: Weight Gain in Patients With Breast Cancer Receiving Adjuvant Treatment as a Function of Restraint, Disinhibition, and Hunger. Oncology Nursing Forum (supp) 17:23-30, 1990.
22. Smets, EMA, Barssen ALJ, Schuster-Uitterhoeve ALJ, et al: Fatigue in cancer patients. British Journal of Cancer 68:220-224,1993.
23. Winningham ML, Nail LM, Burke MB, et al: Fatigue and the cancer ezperience: The state of knowledge. Oncology Nursing Forum 21: 23-26, 1994.
24. Demark-Wahnefried W,Rimer BK, Winer EP. Weight gain in women with breast cancer. J Am Diet Assn. 97:5519-526, 1997.
25. Fortin H, et al: Psychosomatic approach to premenstrual syndrome. Canadian Medical Association Journal 79:978-81, 1958.
26. Foltz AT: Weight Gain Among Stage II Breast Cancer Patients: A Study of Five Factors. Oncology Nursing Forum 12:21-26, 1985.
27. Rose D and Davies T: Ovarian function in patients receiving adjuvant chemotherapy for breast cancer. Lancet 1:1174-6,1977.
28. Morabia A, Szklo M, Sewart W, Schulman L, Thomas DB, Zacur HA: Thyroid hormones and duration of ovulatory activity in the etiology of breast cancer. Cancer Epidemiology, Biomarkers & Prevention 1: 389-93, 1992.
29. Clur A: Di-iodothyronine as part of the oestradiol and catechol oestrogen receptor-- the role of iodine, thyroid hormones and melatonin in the aetiology of breast cancer. Medical Hypotheses 27: 303-11, 1988.
30. Wade GN, Gray JM, Blausten JD: Effects of Estrogens and Antiestrogens on Eating Behavior, Metabolism, and Energy Balance 7(supp):61-68,1993.
31. denBesten C, Vansant G, Westrate JA, et al: Resting Metabolic rate and diet induced thermogenesis in abdominal and gluteal-femoral obese women before and after weight reduction. American Journal of Clinical Nutrition 47:840-847, 1988.
32. Haarbo J, Marslew U, Gotfredson A, et al: Postmenopausal hormone replacement therapy prevents central distrivution of vody fat after menopause. Metabolism 40:1323-1326, 1991.
33. Bisdee JT, James WPT, Shaw MA: Changes in energy expenditure during the menstrual cycle. British Journal of Nutrition 61:187,1989.
34. Solomon SJ, Kurzer MS, Calloway DH: Menstrual cycle and basal metabolic rate in women. American Journal of Clinical Nutrition 36: 611, 1982.
35. Segal Kr, Dunaif A: Resting Metabolic Rate and Postprandial Thermogenesis in Polycystic Ovarian Syndrome. International Journal of Obesity 14:559-67, 1990.
36. Sallis J, Haskell W, Wood P, et al. Physical activity assessment methodology in the Five-City project. Am J Epidemiol. 21:91-106, 1985.
37. McNair DM, Lorr M, Droppleman LF: The Manual for the Profile of Mood States. SanDiego CA: Educational and Industrial Testing Service 1971.
38. Folkman S, Lazarus RS: Analysis of coping in amiddle-aged community sample. Journal of Health and Social Behavior 21: 219-239, 1980.

APPENDIX 1

WEIGHT GAIN IN BREAST CANCER PATIENTS ON CHEMOTHERAPY. EXPLORING HORMONAL, BODY COMPOSITION AND BEHAVIORAL MECHANISMS.

Nagi Kumar, Diane Riccardi, Kathy Allen, Alan Cantor, Paul Jacobsen, , John Horton, Susan Minton, Lodivicco Balducci, Gary Lyman.

H. Lee Moffitt Cancer Center & Research Institute. University of South Florida. Tampa, FL 33612-9497

Kumar@moffitt.usf.edu

The purpose of the study is to observe the relative contribution of thyroid function, sex-hormonal levels, physical activity, psychological state and nutritional intake on changes in body weight in a group of breast cancer patients, receiving adjuvant chemotherapy. Women scheduled to receive adjuvant chemotherapy were assessed prior to their first infusion and followed until the end of treatment and changes in weight, body composition, physical activity, nutritional intake, fatigue, sex-hormones, thyroid hormones and ways of coping were observed.

Fifty-three subjects completed the study during the first year. Preliminary results indicate that the average age of this cohort is 48.96 years, 43.9% were smokers, 48% had a family history of breast cancer, 56% reported increased fatigue and 55% gained weight during chemotherapy. Hyperphagia was observed during treatment, with percent fat intake increasing from 26% to 30.2% by the end of therapy. However, we observed a significant decrease in the average hours worked from 33.4 hours per week to 12.7 hours by the end of therapy. Fifty five percent of the subjects were pre-menopausal at baseline, but all patients were amenorrheic at the completion of therapy with 72.5% showing a significant decrease in serum total estradiol levels post therapy. Thyroxine-binding-globulin levels were elevated in 68.8% of the subjects after therapy while Triiodothyronine-3 uptake levels were decreased indicative of lowered thyroid function.

Based on the preliminary observations, weight gain in breast cancer patients may be a phenomenon resulting from hormonal and lifestyle changes and offers an opportunity for prevention and improved prognosis.

The U.S. Army Medical Research and Material Command under DAMD-17-98-1-8240 supported this work.

Weight Gain in Breast Cancer Patients on Chemotherapy

NB Kumar, Ph.D., K Allen, R.D., A Cantor, Ph.D., P Jacobsen, Ph.D., J Horton, M.D., S Minton, M.D., & L Balducci, M.D.
H. Lee Moffitt Cancer Center & Research Inst., Tampa, Florida

Prevalence and Magnitude of Weight Gain in Breast Cancer Patients During Chemotherapy

- Between 5-50 lbs weight gain has been consistently reported by patients during treatment
  50-95% patients reported weight gain
- More common in pre-menopausal than post-menopausal patients
- Common in patients receiving multi-agent therapies
  The longer the duration of therapy - the greater the weight gain
  Weight gain is observed irrespective of stage of disease

Consequences of Weight Gain

- Obesity at diagnosis - adverse prognostic indicator
- Obesity in node positive postmenopausal Breast Cancer patients - adverse prognostic indicator
- Risk of recurrence - 1.33-1.5 times higher - obese vs non-obese
- 1.6 times greater risk of death in gainers vs non-gainers

Specific Aim:

- The purpose of the study is to observe the relative contribution of thyroid function, sex-hormonal levels, physical activity, psychological state and nutritional intake on changes in body weight in a group of breast cancer patients, receiving adjuvant chemotherapy.

Research Design:

- 200 Women scheduled to receive adjuvant chemotherapy were assessed prior to their first infusion and followed until the end of treatment and changes in weight, body composition, physical activity, nutritional intake, fatigue, sex-hormones, thyroid hormones and ways of coping were observed.

Preliminary Results: Demographic and Lifestyle Variables (n = 53/Year 1)

Variables	Percentage/Number
Average Age	48.9 Years
Smokers	43.9%
Family Hx of Breast Cancer	48%
Patients reporting fatigue during treatment	56%
Patients reporting weight gain during treatment	55%
Patients reporting hyperphagia during treatment	100%

Preliminary Results: Changes in lifestyle and hormonal variables from baseline to post treatment

Variables	Baseline	Post Treatment
Average fat intake	26%	30.2%
Average number of hours worked	33.4 hours	12.7 hours
Number of subjects menstruating	22	0

Preliminary Results: Changes in hormonal levels from baseline to post-treatment

Variables	Percentage of patients indicating change
Decrease in serum total estradiol	72.5%
Increase in Tyroxine-binding globulin	68.8%
Decrease in Triiodothyronine-3 uptake	68%

Conclusions:

- Based on the preliminary observations, weight gain in breast cancer patients may be a phenomenon resulting from hormonal and lifestyle changes and offers an opportunity for prevention and improved prognosis.

- Research Funded by: The U.S. Army Medical Research and Material Command under DAMD-17-98-8240

APPENDIX 3

NAGI KUMAR, Ph.D., R.D.

H. Lee Moffitt Cancer Center & Research Institute. University of South Florida.
Tampa, FL 33612-9497

Manuscripts, Abstracts & Presentations:

Abstract submitted for Podium Presentation:
WEIGHT GAIN IN BREAST CANCER PATIENTS ON CHEMOTHERAPY. EXPLORING HORMONAL, BODY COMPOSITION AND BEHAVIORAL MECHANISMS.Nagi Kumar, Diane Riccardi, Kathy Allen, Alan Cantor, Paul Jacobsen, John Horton, Susan Minton, Lodivicco Balducci, Gary Lyman. H. Lee Moffitt Cancer Center & Research Institute. University of South Florida. Proceedings of the 5th International Symposium on Predictive Oncololgy & Therapy. November 2-5, 2000.

The U.S. Army Medical Research and Material Command under DAMD-17-98-1-8240 supported this work.

WEIGHT GAIN IN BREAST CANCER PATIENTS ON CHEMOTHERAPY. EXPLORING HORMONAL, BODY COMPOSITION AND BEHAVIORAL MECHANISMS.

Nagi Kumar, Diane Riccardi, Kathy Allen, Alan Cantor, Paul Jacobsen, , John Horton, Susan Minton, Lodivicco Balducci, Gary Lyman.

H. Lee Moffitt Cancer Center & Research Institute. University of South Florida. Tampa, FL 33612-9497

The purpose of the study is to observe the role of hormonal function, physical activity, mental state and nutritional intake on changes in body weight in a group of breast cancer patients, receiving adjuvant chemotherapy.

Women scheduled to receive chemotherapy were evaluated prior to their first treatment and followed until the end of treatment and changes in weight, body composition, physical activity, nutritional intake, fatigue, hormones and ways of coping were observed.

Fifty-three subjects completed the study during the first year. Preliminary results show that the average age of this group was 48.96 years, 43.9% were smokers, 48% had a family history of breast cancer, 56% reported increased fatigue and 55% gained weight during chemotherapy. Patients increased their consumption of food, specifically fat, with percent fat intake increasing from 26% to 30.2% by the end of therapy. However, the average hours worked decreased from 33.4 hours per week to 12.7 hours by the end of therapy. Fifty five percent of the subjects were pre-menopausal at baseline, but all patients stopped having their menses at the completion of therapy with 72.5% showing a decrease in sex-hormone levels post therapy. Thyroid hormone levels were decreased indicative of lowered thyroid function.

Based on the preliminary observations, weight gain in breast cancer patients may be a result of hormonal and lifestyle changes that occur as a result of treatment. As the cause of weight gain is preventable, by educating and counseling patients during treatment, weight gain in breast cancer patients can be prevented, thereby improving prognosis.

APPENDIX 4

Android Obesity at Diagnosis and Breast Carcinoma Survival

Evaluation of the Effects of Anthropometric Variables at Diagnosis, Including Body Composition and Body Fat Distribution and Weight Gain during Life Span, and Survival from Breast Carcinoma

Nagi B. Kumar, Ph.D., R.D.[1,2]
Alan Cantor, Ph.D.[2]
Kathy Allen, R.D.[1,3]
Charles E. Cox, M.D.[3]

[1] Department of Nutrition, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida.

[2] Department of Cancer Control, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida.

[3] Department of Surgery, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida.

The authors thank Janelle Perkins, Pharm.D., for her assistance with the data analysis. In addition, we thank Helen Lewis, Tumor Registrar, for her assistance with data retrieval.

Address for reprints: Nagi B. Kumar, Ph.D., R.D., Department of Nutrition, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida 33612-9497.

Received December 9, 1999; accepted February 14, 2000.

BACKGROUND. Although a large body of research exists concerning pathologic prognostic indicators of the rate of incidence and survival from breast carcinoma, to the authors' knowledge very few studies have examined the effects of anthropometric variables such as height, obesity, weight gain in adulthood, timing of weight gain, and body composition to survival, although these variables are related to the incidence rate.

METHODS. The survival status of 166 patients diagnosed with primary breast carcinoma and followed for at least 10 years was obtained from the Cancer Center's registry, and significant anthropometric and other known prognostic indicators regarding survival after diagnosis were determined by Cox proportional hazards analysis.

RESULTS. Eighty-three of 166 breast carcinoma patients (50%) with up to 10 years of follow-up died of disease. Android body fat distribution, as indicated by a higher suprailiac:thigh ratio, was a statistically significant ($P < 0.0001$) prognostic indicator for survival after controlling for stage of disease, with a hazards ratio of 2.6 (95% confidence interval [95% CI], 1.63–4.17). Adult weight gain, as indicated specifically by weight at age 30 years, was a statistically significant ($P < 0.05$) prognostic indicator for survival with a hazards ratio of 1.15 (95% CI, 1.0–1.28). In addition, the authors observed the Quatelet Index, a negatively significant ($P < 0.01$) prognostic indicator for survival with a hazards ratio of 0.92 (95% CI, 0.87–0.98). Other markers of general obesity such as weight at diagnosis, percent body fat, and body surface area were not significant markers influencing survival. Similarly, height; triceps, biceps; subscapular, suprailiac, abdominal, and thigh skinfolds; waist and hip circumferences; family history; and reproductive and hormonal variables at the time of diagnosis showed no apparent significant relation to survival.

CONCLUSIONS. The results of the current study provide some evidence that android body fat distribution at diagnosis and increased weight at age 30 years increases a woman's risk of dying of breast carcinoma. ***Cancer* 2000;88:2751–7.**
© 2000 American Cancer Society.

KEYWORDS: breast carcinoma, survival, android obesity.

It is estimated that more than 175,000 new cases of female breast carcinoma will be diagnosed in the United States in 1999, and 43,900 persons will die of this disease.[1] Most of these patients will be diagnosed with Stage I or II disease, and a significant proportion of these women will be treated with chemotherapy in addition to surgery and/or radiation therapy. Although more women are diagnosed at earlier stage of disease and research has provided numerous treat-

ment options, significant international differences in survival rates from breast carcinoma exist, with greater survival rates observed in Japanese women[2] as compared with women in Western civilizations, which cannot be explained by extent of disease nor therapies used.[3]

Although a large body of research exists in the area of pathologic prognostic indicators of incidence rate, prognosis, and survival from breast carcinoma, very few studies have examined comprehensively the effects of anthropometric variables on survival. Anthropometric variables such as height, obesity,[4–9] weight gain in adulthood, timing of weight gain, and body composition[10–15] have been known to increase risk of breast carcinoma incidence. Whereas several researchers have reported poor prognosis in obese breast carcinoma patients[11,16–25] with a risk of disease recurrence 1.33–1.5 times higher in obese than nonobese,[24,25] others have not observed this relation,[26–28] specifically among premenopausal breast carcinoma patients.[29] Possible mechanisms for the association of indicators of obesity to breast carcinoma risk include elevated levels of endogenous estrogen, which has been associated with efficient conversion androstenedione to estrone in peripheral adipose tissue,[16,18] insulin resistance,[29,30] or subnormal levels of progesterone. Although obese women may be at higher risk for developing breast carcinoma, we and others have shown that women with a predominant android body fat distribution are a subset of women who are at a significantly higher risk for this disease.[12,13,15,18,30,31] We and others also have shown that women who progressively gain weight during adulthood, which is predominantly android,[10,14,15,30–32] are at higher risk for breast carcinoma. Although it may be critical to examine risk factors that contribute to breast carcinoma incidence rates, it may, in addition, be important to consider the theory that factors influencing the occurrence of breast carcinoma also may affect subsequent course of the disease and thus survival. In the current study, our specific objective was to evaluate the effects of anthropometric variables at diagnosis, including body composition and body fat distribution as measured by skinfold and circumference measurements, in addition to obesity and survival from breast carcinoma. In addition, we investigated the association of history of weight and weight gain from adolescence to adulthood, before diagnosis, and its effect on disease survival in this cohort of breast carcinoma patients.

SUBJECTS AND METHODS

The subjects in our cohort included a total of 166 primary breast carcinoma patients consecutively recruited and followed in a case–control study at the H. Lee Moffitt Cancer Center and Research Institute. All patients admitted to the study were diagnosed within 3 months of entry to the study and had not been treated with adjuvant hormonal therapy or chemotherapy. The criteria for exclusion of patients were as follows: pregnancy, weight loss of more than 10% of usual weight, having engaged in a dietary or therapeutic regimen for weight loss during the year preceding the study, being on a cholesterol lowering therapeutic regimen, or having a medical condition or physical stature (weight > 220 lbs) that limited or prevented the researchers from obtaining accurate skinfold measurements. After receipt of informed consent, information regarding subjects medical history; clinical and pathologic diagnosis; previous and current medications taken; hormonal histories, including exogenous and endogenous events, such as hormonal supplement use, timing of menopause and menarche and reproductive history; cigarette and alcohol use; and family history of cancer were obtained using an epidemiologic questionnaire. We obtained anthropometric measurements from all 166 subjects admitted to this study. The anthropometric measures obtained at diagnosis included height (inches), weight (lbs), skinfold measurements (mm) in predetermined sites such as biceps, triceps, subscapular, midaxillary, suprailiac, abdomen and thigh, and circumference measurements (inches) such as waist and hip. These standards and methods previously were described, and the results were published.[18] Weight histories from all 166 patients in the cohort at ages 16, 20, 30, and 40 years were obtained using methods previously described and published.[11] The study cohort was followed for 10 years through annual or more frequent contact by the Cancer Center. Recurrence of cancer was confirmed by clinical or pathologic assessment, and survival status date of last contact was obtained from the cancer center's tumor registry between March and July 1997. The demographic and pathologic characteristics of this cohort are outlined in Tables 1 and 2, respectively.

Statistical Analysis

The distributions of known risk factors for breast carcinoma such as age at menarche, menopause, age at first childbirth, family history of cancer, cigarette and alcohol use, and parity were assessed in addition to anthropometric variables, such as weight history, obesity, and body fat distribution at diagnosis. Significant prognostic indicators of survival after diagnosis were

TABLE 1
Demographic Data for Patients with Breast Carcinoma

Variables	Breast carcinoma patients (n = 166) (%)
Age	
< 40	13
41–50	26
51–60	23
> 60	38
Race	
White	92
Black	4
Hispanic/other	4
Age at menarche (yrs)	
8–11	24
12–14	65
> 14	11
Menopausal status	
Premenopausal	17
Postmenopausal	83
Number of children	
0	20
1–3	60
≥ 4	20
Smoker	
Yes	40
No	60

TABLE 2
Pathologic Data for Patients with Breast Carcinoma

Variables	Breast carcinoma patients (n = 166) (%)
Stage of disease	
Not available	14
Stage I	33
Stage II	41
Stage III	9
Stage IV	3
Lymph nodes	
Positive	36
Negative	64
Site of recurrence	
Bone	43
Chest wall	16
Liver	14
Lung	9
Other	27

determined by Cox proportional hazards analysis. After stratifying for stage, all covariates were evaluated univariately. Then, a stepwise selection method was used with entry and staying criteria of 0.05. Significant covariates then were categorized to evaluate adjusted risk ratios compared with a baseline group by using Cox proportional hazards.

TABLE 3
Proportional Hazards Regression Analysis Body Mass Indices and Breast Carcinoma Survival

Variable	Risk ratio	95% CI	*P* value
Suprailiac: thigh ratio	2.61	(1.63–4.17)	< 0.001
Weight at age 30 yrs	1.15	(1.01–1.28)	0.036
Quatelet index	0.92	(0.87–0.98)	0.07

CI: confidence interval.

RESULTS

Eighty-three of 166 breast carcinoma patients with up to 10 years of follow-up failed to survive. The final model of the multivariate analysis of survival determinants is shown in Table 3. Android body fat distribution, as indicated by higher suprailiac:thigh ratio, was a statistically significant ($P < 0.0001$) prognostic indicator for survival after controlling for stage of disease, with a hazards ratio of 2.6 (95% confidence interval [CI], 1.63–4.17 Adult weight gain, as indicated specifically by weight at age 30 years, was a statistically significant ($P < 0.05$) prognostic indicator for survival with a hazards ratio of 1.15 (95% CI, 1.0–1.28). Estimated breast carcinoma survival rates by suprailiac: thigh ratio and weight at age 30 years were plotted (Figures 1 and 2). In addition, we observed Quatelet Index [weight(kgs)/height(m)2], a negatively significant ($P < 0.01$) prognostic indicator for survival with a hazards ratio of 0.92 (95% CI 0.87–0.98). Other markers of general obesity such as weight at diagnosis, body fat percentage, and body surface area were not significant markers influencing survival. Similarly, height, triceps, biceps, subscapular, suprailiac, abdomen, thigh skinfolds, waist and hip circumferences, family history, and reproductive and hormonal variables at diagnosis showed no significant relation to survival.

DISCUSSION

This study clearly indicates that a predominant android body fat distribution at diagnosis and weight at age 30 years, which is indicative of adult weight gain and which is predominantly android in distribution, are two factors that are as important as predictors of survival as they are to risk of breast carcinoma. Quatelet Index, which is an indicator of body size, including the variables of height and weight, was negatively correlated with survival. The results of our study thus indicate that anthropometric factors influencing the occurrence of breast carcinoma may, in fact, also affect subsequent course of the disease and thus survival. To our knowledge, our study was the first of its

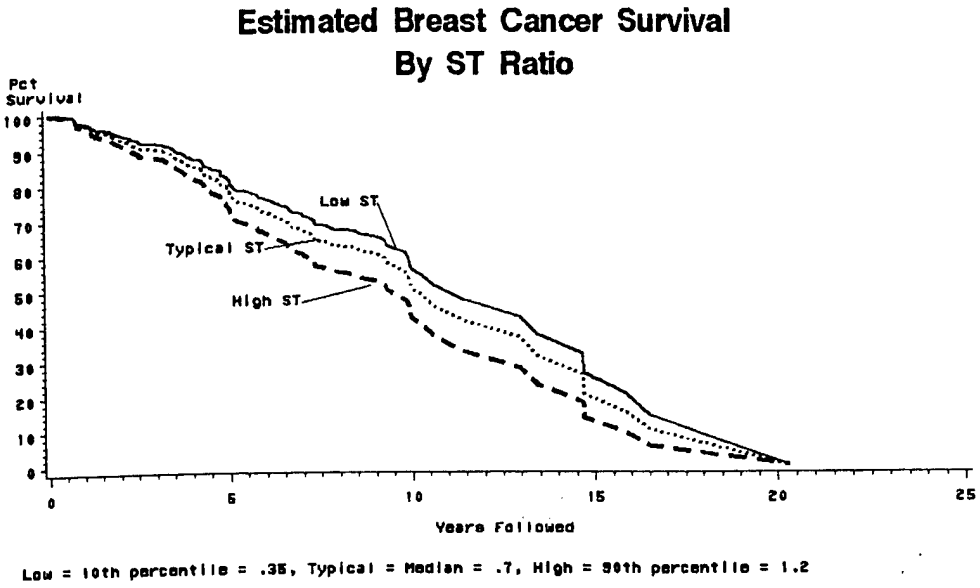

FIGURE 1. Estimated breast carcinoma survival by ST ratio. Pct survival: percent survival.

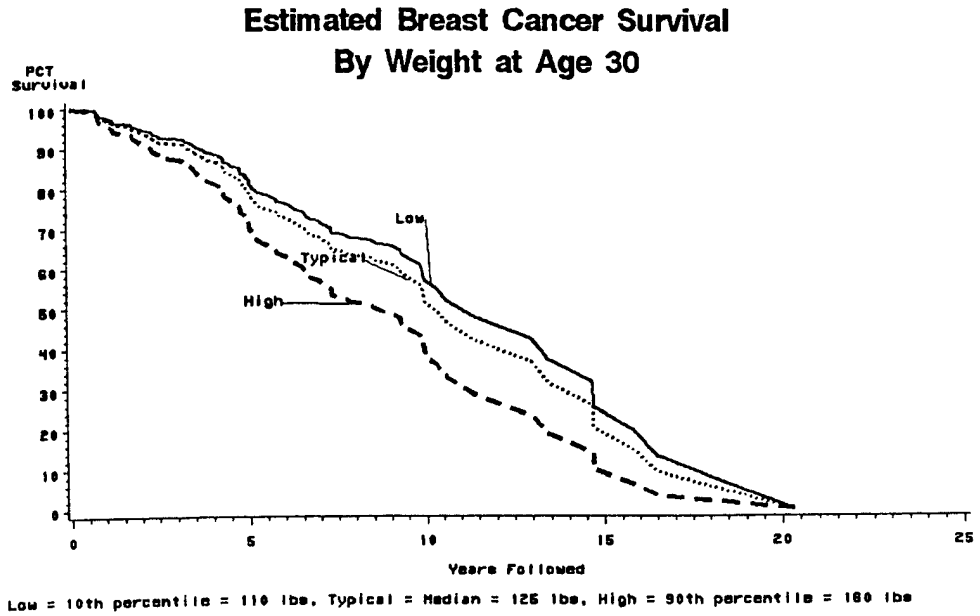

FIGURE 2. Estimated breast carcinoma survival by weight at age 30 years. Pct survival: percent survival.

kind to systematically examine the association of fat distribution, as measured by the distribution of skinfold (suprailiac:thigh) and circumference (waist:hip) measures, with survival of breast carcinoma patients, in addition to indicators of obesity. Only one other study,[27] previous to our current work, addressed the association between body fat distribution and breast carcinoma survival. However, as the investigators observe, the study found no association because they did not measure any lower body fat distribution parameters and recommend the use of these measures to determine if the patient had a predominantly android or gynoid body fat distribution. In two other studies[27,33] examining the contribution of anthropometric measures to survival, higher premorbid triceps skinfold and subscapular[27] skinfold measurements increased a woman's risk of dying from breast carcinoma. However, the ratio of upper:lower body fat distribution, which would be indicated by the ratio of upper and lower body skinfold or circumference measurements, was not addressed nor measured. Although it may be argued that high triceps and subscapular measurements may be correlated with increased android body fat distribution,[27,33] it would be important to determine the relative ratio of upper and lower skinfold (suprailiac:thigh) or circumference (waist:hip) measurements to show the predominance of gynoid or android distribution more accurately. As with results obtained in our previous study with timing of weight gain and breast carcinoma risk,[11] these

results indicate that weight at age 30 years, indicative of adult weight gain, was a variable correlated with not only increased risk for developing breast carcinoma, but in addition, a higher risk for mortality in breast carcinoma patients. Although we examined the variables of weight at ages 16, 20, 30, and 40 years and weight gain between these ages in this cohort, the variable of weight at age 30 years was the only statistically significant variable contributing to risk of survival in our study. Again, this is the first study to our knowledge to examine the effect of adult weight and subsequent risk of breast carcinoma and death. Weight gain during periods of hormonal change, such as puberty, pregnancy, lactation, and menopause may have different biologic effects, perhaps because of differences in the location of body fat during these periods. Weight gain during pubescent years is primarily in the hips and buttocks (gynoid); however, weight gain during adult years including during pregnancy and menopause has been characterized by central body fat distribution (android)[14,15,29–32,34–36] In addition, as lean body mass decreases with age,[37] adult weight gain largely reflects gain in body fat. Hence, adult weight gain largely reflects gain in body fat and, unlike the gain in gynoid body fat distribution in puberty, is predominantly android[14,15,30–32] and has similar implications as with women having a predominant android body fat distribution, thus theoretically posing a higher risk of breast carcinoma and survival.

The physiologic mechanism of the two indicators observed—android obesity at diagnosis and weight at age 30 years—in our study is related to and is most likely a consequence of adult weight gain. The metabolic and hormonal abnormalities noted in obesity are more pronounced in individuals with upper body predominance. Although chronic disease is most commonly found in obese women, women with android obesity have been noted to have a higher risk of breast and endometrial carcinomas ,[18,38–40] longer menstrual cycles, and an increased incidence rates of hirsutism, gall bladder disease, hypertension, atherosclerosis, insulin resistance, and noninsulin-dependent diabetes mellitus, than women of the same weight with a gynoid obesity.[17,29,30,41–49] We and others have shown elevated nonprotein bound estradiol and lower sex hormone binding globulin (SHBG) levels in patients with breast carcinoma compared with age-matched controls.[50–53] The SHBG levels decreased with increasing abdominal body fat localization or android obesity. Conversely, studies have reported significant rise in SHBG levels and a decrease in unbound biologically active estrogens with decrease in weight in both[51–53] pre- and postmenopausal women. It can be theorized that, just as in increasing risk of breast carcinoma, android body fat predominance results in increased exposure to biologically active unbound fractions of estrogens even after diagnosis of breast carcinoma and may stimulate growth of preexisting neoplastic lesions,[54] thus increasing the risk of death from breast carcinoma. In Western populations, evidence of abdominal obesity associated with hyperinsulinemia increases progressively after age 40 years. It has been demonstrated that weight gain leading up to menopause mainly involves android body fat distribution that is associated with insulin resistance that may act as late stage promoters of mammary carcinogenesis.[29,30] In addition, the results of the study indicated a negative correlation of Quatelet Index, which takes into consideration both variables of height and weight, with survival. Of note, these are two variables that previously have been positively correlated with survival from breast carcinoma, which may indicate that android body fat distribution and not obesity is a more critical prognostic anthropometric indicator related to survival from breast carcinoma. Thus, the specific population of women who progressively gain weight during their adult years and whose body fat distribution is predominantly android are not only at greater risk for breast carcinoma but, in addition, at risk of death from breast carcinoma.

FUTURE DIRECTIONS

Our study was the first to our knowledge to thoroughly examine and determine the association between body fat distribution and adult weight gain at diagnosis as risk for survival from breast carcinoma. Android obesity and weight gain in adulthood are all modifiable risk factors and thus present the greatest implication for prevention of recurrence and thus death in this population. Android obesity is most conducive to reduction by simply modifying lifestyle factors such as diet and exercise.[52,55,56] Reduction in android obesity produced increases in SHBG levels and decreases in free estradiol.[53] Because android obesity is a consequence of adult weight gain, guidelines from the American Institute of Cancer Research[57] recommending that adult weight gain must not exceed 11 pounds must be taken more seriously. Family practitioners and gynecologists are in an ideal position to recommend aggressive interventions with weight loss and management, specifically for those patients who present with risk factors for breast carcinoma. Incorporating a simple, reliable waist:hip circumference measurement in breast carcinoma screening centers and family practitioners' and gynecologists' offices may enable us to identify this subgroup of women. In addition, once breast cancer is diagnosed, it may be ideal to identify this subgroup of breast carcinoma

patients and provide intervention strategies to control or reduce weight gain thus influencing hormonal status and survival. Certainly, future prospective intervention studies aimed at reducing android obesity in breast carcinoma patients and examining prognosis and survival are well justified. Interventions directed at weight control may have a substantial effect not only on breast carcinoma mortality but may have a substantial effect on mortality associated with other chronic illnesses such as heart disease and diabetes.

REFERENCES

1. American Cancer Society, Inc. Cancer facts and figures—1999. Atlanta, GA: ACS Publications.
2. Kyogoku S, Hirohata T, Takeshita S, Nomura Y, Shigematsu T, Horie A. Survival of breast cancer patients and body size indicators. *Int J Cancer* 1990;46:824–31.
3. Morrison AC, Lowe CR, MacMahon B, Ravnihar B, Yuasa S. Some international differences in treatment and survival in breast cancer. *Int J Cancer* 1976;18:269–73.
4. van den Brandt PA, Dirx MJ, Ronckers CM, van den Hoogen P, Goldbohm RA. Height, weight, weight change, and post menopausal breast cancer risk: the Netherlands Cohort Study. *Cancer Causes Control* 1997;8:39–47.
5. Pujol P, Galtier-Dereure F, Bringer J. Obesity and breast cancer risk. *Hum Reprod* 1997;12:116–25.
6. Chang S, Buzdar AU, Hursting SD. Inflammatory breast cancer and body mass index. *J Clin Oncol* 1998;16:3731–5.
7. Carroll KK. Obesity as a risk factor for certain types of cancer. *Lipids* 1998;33:1055–9.
8. Stoll BA. Westernized nutrition and the insulin resistance syndrome: a link to breast cancer. *Eur J Clin Nutr* 1999;53: 83–7.
9. Peacock SL, White E, Daling JR, Voight LF, Malone KE. Relation between obesity and breast cancer in young women. *Am J Epidemiol* 1999;15;149:339–46.
10. Vatten LJ, Kvinnsland S. Prospective study of height, body mass index and risk of breast cancer. *Acta Oncol* 1992;31: 195–200.
11. Kumar NB, Lyman GH, Allen K, Cox CE, Schapira DV. Timing of weight gain and breast cancer risk. *Cancer* 1995;76: 243–9.
12. Ballard-Barbash R, Schatzkin A, Carter CL. Body fat distribution and breast cancer in the Framingham study. *J Natl Cancer Inst* 1990;82:286–90.
13. Radimer K, Siskind V, Bain C, Schofield F. Relation between anthropometric indicators and breast cancer among Australian women. *Am J Epidemiol* 1990;131:794–803.
14. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effect of weight and weight gain on breast cancer risk. *JAMA* 1997;278:1407–11.
15. Lovejoy JC. The influence of sex hormones on obesity across the female life span. *J Womens Health* 1998;7:1247–56.
16. Senie R, Rosen P, Rhodes , Lesser M, Kinne D. Obesity at diagnosis of breast carcinomas influences duration of disease-free survival. *Ann Int Med* 1992:116:26–32.
17. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 1996;45:633–8.
18. Schapira DV, Kumar NB, Lyman GH, Cox CE. Abdominal obesity and breast cancer risk. *Ann Int Med* 1990;112:182–6.
19. Verreault R, Brisson J, Deschenes L, Naud F. Body weight and prognostic indicators in breast cancer. Modifying effect of estrogen receptors. *Am J Epidemiol* 1989;129:260–8.
20. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. *Cancer* 1995;76:275–83.
21. Newman SC, Lees AW, Jenkins HJ. The effect of body mass Index and oestrogen receptor level on survival of breast cancer patients. *Int J Epidemiol* 1997;26:484–90.
22. Machle BO, Tretli S. Pre-morbid body mass index in breast cancer:reversed effect on survival in hormone receptor negative patients. *Breast Cancer Res Treat* 1996;41:123–30.
23. Schapira DV, Clark RA, Wolff PA, Jarrett AR, Kumar NB, Aziz NM. Visceral obesity and breast cancer risk. *Cancer* 1994;74: 632–9.
24. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, Veeder MH. Weight change in women treated with adjuvant therapy or observed following mastectomey for node-positive breast cancer. *J Clin Oncol* 1990;8:1327–34.
25. Bastracchea J, Hortobagyi GN, Smith TL, Kau SC. Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. *AnnInt Med* 1993;119:18–25.
26. Obermair A, Kurz C, Hanzal E, Bancher-Todesca D, Thoma M, Bodisch A, et al. et al. The influence of obesity on the disease-free survival in primary breast cancer. *Anticancer Res* 1995;15:2265–9.
27. Tonkelaar I, Waard F, Seidell J, Fracheboud J. Obesity and subcutaneous fat patterning in relation to survival of postmenopausal breast cancer patients participating in the DOM-project. *Breast Cancer Res Treat* 1995;34:129–37.
28. Schapira DV, Wolff PA, Kumar, NB, Anderson JB, Aziz NM, Lyman GH, et al . The effect of weight loss on estimated breast cancer risk and sex hormone levels.*Oncol Rep* 1994; 1:613–7.
29. Stoll BA. Perimenopausal weight gain and progression of breast cancer precursors. *Cancer Detect Prev* 1999;23:31–6.
30. Stoll BA. Timing of weight gain in relation to breast cancer risk. *Ann Oncol* 1995:6:245–8.
31. Magnusson C, Baron J, Persson I, Wolk A, Bergstrom R, Trichopoulos D, et al. Body size in different periods of life and breast cancer risk in post-menopausal women. *Int J Cancer* 1998;76:29–34.
32. Kirchengast S, Gruber D, Santor M, Knogler W, Huber J. The impact of nutritional status on body fat distribution patterns in pre- and postmenopausal females. *J Biosoc Sci* 1998;30: 145–54.
33. Jain M, Miller A. Pre-morbid body size and the prognosis of women with breast cancer. *Int J Cancer* 1994;59:363–8.
34. Smith DE, Lewis CE, Caveny JL, Perkins LL, Burke GL, Bild DE. Longitudinal changes in adiposity associated with pregnancy: the CARDIA study. *JAMA* 1994;271:1747–51.
35. Mueller WH. The changes with age of the anatomical distribution of fat. *Soc Sci Med* 1982;16:191–6.
36. Ohlin A, Rossner S. Maternal body weight development after pregnancy. *Int J Obes* 1990;14:159–73.
37. Forbes GB, Reina JC. Adult lean body mass declines with age: some longitudinal observation. *Metabolism* 1970;19: 653–63.

38. Schapira DV, Kumar NB, Lyman GH, Cavanagh D, Roberts WS, LaPolla J. Upper body fat distribution and endometrial cancer risk. *JAMA* 1991;266:1808–11.
39. Sellers TA, Kushi LH, Potter JD, Kaye SA, Nelson CL, McGovern PG, et al. Effect of family history, body fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. *N Engl J Med* 1992;14;326:1323–9.
40. Ng EH, Gao F, Ji CY, Ho GH, Soo KC. Risk factors for breast carcinoma in Singaporean Chinese women: the role of central obesity. *Cancer* 1997;80:725–31.
41. Hartz AJ, Rupley DC, Rimm AA. The association of girth measurements with disease in 32,856 women. *Am J Epidemiol* 1984;119:71–80.
42. Carranza-Lira S, Murillo-Uribe A, Martinez-Trejo N, Santos-Gonzalez J. Changes in symptoms, blood pressure, glucose, hormones, and lipid levels according to weight and body fat distribution in climacteric women. *Int J Fertil Womens Med* 1998;43:306–11.
43. Guagnano MT, Pace-Palitti V, Carrabs C, Merlitti D, Sensi S. Weight fluctuations could increase blood pressure in android obese women. *Clin Sci* 1999;96:677–80.
44. Neel JV, Julius S, Weder A, Yamada M, Kardia SL, Haviland MB. Sydrome X: is it for real? *Genet Epidemiol* 1998;15:19–32.
45. Wu CH, Yao WJ, Lu FH, Wu JS, Chang CJ. Relationship between glycosylated hemoglobin, blood pressure, serum lipid profiles and body fat distribution in healthy Chinese. *Atherosclerosis* 1998;137:157–65.
46. Secreto G, Zumoff B. Abnormal production of androgens in women with breast cancer. *Anticancer Res* 1994;14:2113–7.
47. Schreier LE, Berg GA, Basillo FM, Lopez GI, Etkin AE, Wikinski RL. Lipoprotein alterations, abdominal fat distribution and breast cancer. *Biochem Mol Biol Int* 1999;47:681–90.
48. Hollmann M, Runnebaum B, Gerhard I. Impact of waist-hip ratio and body mass index on hormonal and metabolic parameters in young, obese women. *Int J Obes Relat Metab Disord* 1997;2:476–83.
49. Tung HT, Tsukuma H, Tanaka H, Kinoshita N, Koyama Y, Ajiki W, et al. Risk factors for breast cancer in Japan, with special attention to anthropometric measurements and reproductive history. *Jpn J Clin Oncol* 1999;29:137–46.
50. Schapira DV, Kumar NB, Lyman GH. Obesity, body fat distribution and sex hormones in breast cancer patients. *Cancer* 1991;67:2215–8.
51. Enriori CL, Osini W, Cremona MD, Etkin AE, Cardillo LR, Eforzo-Membuines J. Decrease of circulating levels of SHBG in post-menopausal obese women as a risk factor in breast cancer:reversible effect of weight loss. *Gynecol Oncol* 1986; 23:77–86.
52. Schapira DV, Kumar NB, Lyman GH. Estimate of breast cancer risk reduction with weight loss. *Cancer* 1991;67: 2622–5.
53. Schapira DV, Wolff PA, Kumar, NB, Anderson JB, Aziz NM, Lyman GH, et al. The effect of weight loss on estimated breast cancer risk and sex hormone levels. *Oncol Rep* 1994; 1:613–7.
54. Morabia A, Wynder EI. Epidemiology and natural history of breast cancer: implications in the body-weight breast cancer controversy. *Surg Clin North Am* 1990;70:739–52.
55. Jones PR, Edwards DA. Areas of fat loss in overweight young females following an 8-week period of energy intake reduction. *Ann Hum Biol* 1999;26:151–62.
56. Stefanick ML. Exercise and weight control. *Exerc Sport Sci Rev* 1993;21:363–96.
57. Food, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, DC: World Cancer Research Fund/ American Institute of Cancer Research, 1997